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PhRMA

February 25, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Re: Docket No. 97D-2068 Draft Guidance for Industry on Submission of Documentation in Drug Applications for Container Closure Systems Used for the Packaging of Human Drugs and Biologics; Recommended changes Applicable to Bulk Container Section VI.B.

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America wishes to submit the following further comments in response to the subject draft guidance:

Item 1: Container Closure systems for on site storage are a cGMP issue as acknowledged in the first sentence of the second paragraph of this section. The next sentence then indicates that the information developed to support on site storage should be "included in the application."

Issue: Contradictory statements are noted above which need clarification. It would be a new requirement to "include" such data in a filing, it is inappropriate and burdensome with no value added for FDA, consumer, or firm.

Recommendation: Reword the section to clearly state bulk containers are a cGMP item, but that any bulk container and any proposed hold time should be described and justified. This information should be available to the field inspector upon request.

Item 2: Paragraph three deals with shipping bulk product to a contract packager and indicates a post approval commitment would be required to support the container.

Issue: When a firm retains ownership of a product and ships to another site or to a contract packager, the responsibility for developing supportive information is same as noted in Item 1. This is a cGMP area and does not require filing the information or providing any post approval commitment.

Recommendation: Reword section. Perhaps incorporate into previous paragraph. A marked up version of the relevant Sections of the Draft Guidance with suggested revised language is attached.

Thank you for your consideration of these comments.

Sincerely

Thomas X. White

Attachment

97D-0268

C32

Guidance for Industry

Container Closure Systems for Packaging Human Drugs and Biologics

CHEMISTRY, MANUFACTURING, AND CONTROLS DOCUMENTATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
May 1999

VI. BULK CONTAINERS

A. Containers for Bulk Drug Substances

No change

B. Containers for Bulk Drug Products

A container closure system for bulk drug products may be used for storage prior to packaging or for shipment to repackagers or contract packagers. In all cases, the container closure system should adequately protect the dosage form and should be constructed of materials that are compatible and safe.

Container closure systems for on-site storage have generally been considered a CGMP issue under 21 CFR 211.65. ~~However, if~~ If a firm plans to hold bulk drug products in storage and /or plans to ship product to a their own packaging facility or to a contract packager,, then the container closure system and the maximum storage time should be described and justified ~~in the application~~. In addition, ~~stability~~ data should be ~~provided~~ developed to ~~to~~ demonstrate that extended storage in the described containers does not adversely affect the dosage form. These data should be available for inspection at the site. Even when the storage time before packaging will be short, a firm should use a container closure system that provides adequate protection and that is manufactured from materials that are compatible and safe for the intended use (see section III.B)

~~A container closure system for the transportation of bulk drug products to contract packagers (section II.C.3) should be described in the application.~~ The container closure system should be adequate to protect the dosage form, be constructed with materials that are compatible with product being stored, and be safe for the intended use.

If changes are made to the bulk container closure system initially developed for the product, then the changes should be evaluated for impact to the previously established maximum storage time. Changes should be described, justified and where appropriate new data developed for the bulk container. These data should be available for inspection at the site .~~The protective properties of the shipping container are verified by the practice of including annual batches of the packaged product in postapproval stability studies.~~

A container closure system specifically intended for the transportation of a large volume of drug product to a repackager (section II.C.3), whether for a solid or liquid dosage form, is considered a market package. The package should meet the same requirements for protection, compatibility, and safety as a smaller market package; should be included in the stability studies for application approval and in the long term stability protocol; and should be fully described in the application. The length of time that the dosage form will spend in the bulk container may be a factor in determining the level of detail of the supporting information. Two examples of a large-volume shipping package are a 10,000-tablet HDPE pail with tamper-evident closure, and a 10-liter polyethylene terephthalate (PET) container with a screw cap closure with dispenser attachment for a liquid drug

product. Both are intended for sale to a mass distribution pharmacy. A special case is the pharmacy bulk package which is described in USP <1>.

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